Newly designed molecule blocks chlamydia bacteria

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Researchers at Duke University Medical Center have discovered a way to block the damaging actions of *Chlamydia*, the bacteria responsible for the largest number of sexually transmitted infections in the United States.

The team, which included Duke University microbiologists and chemists, designed a molecule that takes away the bacteria's self-defense mechanisms.

The therapies that could come from this discovery mark a new type of antimicrobial approach. Instead of directly killing the bacteria, they will disarm a central weapon of Chlamydia, and let the body take care of the rest.

Chlamydia infections are symptomless at the beginning, but can become chronic in women and lead to pelvic inflammatory disease and infertility as it infects cells in the uterus and fallopian tubes. It's generally harmless to men. While these infections can be treated with antibiotics, *Chlamydia* can be easily reacquired and arise as a greater problem again. There are more than nearly 3 million new cases in the U.S. each year.

A virulence factor that *Chlamydia* produces, called CPAF, emerged as a promising target to shut down because it plays an important role in protecting the bacteria within hiding places (vacuoles) in human cells. CPAF also prevents the human cell from committing suicide when it senses that it has been invaded by a pathogen (a common self-defense mechanism), giving *Chlamydia* bacteria an extended chance to multiply and stay hidden.

The study was the cover story in the July 21 print edition of Cell Host and Microbe.

Microbiologists and genetics experts led by Raphael Valdivia, Ph.D., an associate professor in the Duke Department of Molecular Genetics and Microbiology, completed the work that narrowed down the search to an enzyme that *Chlamydia* produces, a protease called CPAF.

"*Chlamydia* makes this master protease that takes over the whole cell and prevents it from mounting an effective, pathogen-killing immune response," Valdivia said. "*Chlamydia* is unique among pathogens, in that it can co-exist within humans without causing symptoms for a long time. This reflects a careful balance between the host and the pathogen. We think CPAF is central to this balance. Therefore, if we disarm it, we can tilt the equation toward the human host and mount an effective immune response that will not only clear the infection but prevent it from re-emerging."

The Duke chemists, led by Dewey McCafferty, Ph.D., a professor in the Duke Departments of Chemistry and Biochemistry, designed a molecule that could block the CPAF activity inside of human cells.

"Typically, to design a potent, specific, and cell-permeable inhibitor is a complicated undertaking and inhibitor designs don't work right away," McCafferty said. "But in this case, it worked on the first try. Professor Valdivia's group of microbiologists and my group of chemical biologists worked to establish which qualities we needed to incorporate into a CPAF inhibitor. The results are very exciting, because we have an inhibitor lead molecule that may form the basis for a new class of anti-Chlamydial drugs."

They found that when CPAF was blocked over time by their designed molecule, the protective home that the bacteria make for themselves within the infected cells degraded, and CPAF no longer could degrade the proteins in the cell that would normally mount an immune response to the infection.

When CPAF is inhibited, the infected human cells effectively "commit suicide," Valdivia said. "When

the infected human cell dies, so does *Chlamydia*, and this ends the infection."

Valdivia said that the findings could yield new therapeutic approaches that might turn a natural infection into a vaccination.

"By stopping the cloaking response of the bacteria, we are essentially revealing where they are in the cell and allowing our own immune system to take over and destroy the pathogens," McCafferty said.

Provided by Duke University Medical Center